REMARKS

Upon entry of the previously-filed Amendment Under 37 C.F.R. § 1.116 dated September 5, 2003, claims 21-30 and 38 are pending in the application. Claims 26-28 have been withdrawn from consideration. Applicants respectfully submit that claims 26-28 should be allowable upon allowance of generic claim 21 from which they depend.

Each of the rejections maintained in the Advisory Action of September 30, 2003 is addressed individually below.

Rejection of claims 21-22 and 24-25 under 35 U.S.C. § 103(a)

In the Advisory Action, the Examiner maintained the rejection of claims 21-22 and 24-25 under 35 U.S.C. § 103(a) as allegedly being obvious over Shishikura et al., U.S. Patent No. 6,133,258 ("Shishikura") in view of Csuzdi et al., WO 97/28163 ("Csuzdi"). Applicants respectfully traverse this rejection.

To support a *prima facie* case of obviousness, the cited references must teach or suggest every element of the claimed invention, and must provide a reasonable expectation of success in achieving the claimed invention. MPEP § 2142.

Applicants' claims 21-22 and 24-25 are directed to methods of treating a demyelinating disorder by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex.

The teachings of the primary reference, Shishikura, are addressed in the second declaration of Terence Smith, one of the co-inventors, that is submitted herewith. Dr. Smith's second declaration describes fundamental differences between Applicants' claimed invention and the teachings of Shishikura that render Applicants' claims non-obvious over the cited art. These comments are in addition to those contained in Dr. Smith's first declaration, which was submitted with the Amendment Under 37 C.F.R. § 1.116 filed on September 5, 2003.

As described in Dr. Smith's second declaration, Shishikura deals with kainic acid neuronal excitoxicity and protection against it. The reference describes pyridothiazine derivatives that provide potent inhibition of kainic acid neurotoxicity and anticonvulsant effect against seizure, and therefore are useful as agents for treating

neurological disorders, including multiple sclerosis (*see, e.g.*, column 2, lines 39-59; column 15, lines 43-53). Shishikura uses the effectiveness of pyridothiazine derivatives against seizures and against kainic acid excitotoxicity, which do not belong to the symptomatology of demyelinating disorders, as evidence for usefulness in the treatment of multiple sclerosis. Multiple sclerosis is included in the list of treatable disorders disclosed by Shishikura because its symptomatology includes spasticity (which is not necessarily associated with other demyelinating disorders), and AMPA antagonists were known to have muscle relaxant activity. Shishikura does not recognize that multiple sclerosis is a demyelinating disorder, and does not claim usefulness for therapy of such disorders.

Applicants' invention is directed to the therapy of demyelination and the resulting cell death in demyelinating disorders, rather than direct neuroprotection against excitotoxicity induced by kainic acid or glutamate in neurological disorders as disclosed by Shishikura. There is no known relationship between excitotoxicity and cell death due to demyelination. The mechanisms leading to demyelination are not known, and the literature does not teach that signs of excitotoxic cell death are seen in human tissue or tissue from animal models of demyelinating disorders (*e.g.*, EAE models). Therefore, it is not obvious that any compound which protects cells against excitotoxicity induced by kainic acid or against seizures as disclosed in Shishikura may be useful in therapy of demyelinating disorders, including multiple sclerosis.

Notably, Shishikura does not mention demyelinating disorders, since at that time it was not obvious to the authors that the disclosed compounds could be useful for therapy of demyelinating disorders. Indeed, by using multiple sclerosis as an example of a neurological disorder and not using the term "demyelinating disorders," Shishikura itself provides evidence that it was not obvious for a person of ordinary skill in the art to suspect usefulness of AMPA antagonists in therapy of demyelinating disorders. Similarly, since it is not obvious that an action against seizures and kainic acid neurotoxicity can be useful in therapy of demyelinating disorders, Shishikura did not claim usefulness of pyridothiazine derivatives against demyelinating disorders.

In sum, as established by Dr. Smith's declaration, it simply is not obvious that a person of ordinary skill in the art could conclude from Shishikura's disclosure of the usefulness of pyridothiazine derivatives in treatment of "Huntington's chorea, Parkinson's disease, epilepsy, Alzheimer's disease, senile dementia, cerebral ischemia, anoxia, diabetes, hypoglycemia, drug dependence, head injury, amyotrophic lateral sclerosis and multiple sclerosis" due to "inhibitory action against kainic acid neurotoxicity and anticonvulsant effect for ... seizure" (column 15, lines 43-53) that the disclosed compounds are useful in therapy of demyelinating disorders. Shishikura simply does not teach or suggest that the disclosed compounds would be useful for treating demyelination in multiple sclerosis patients, and does not provide any enabling disclosure regarding how the disclosed compounds might be used to treat demyelinating disorders. Thus, for the reasons set forth above and discussed in Dr. Smith's declaration, Shishikura's inclusion of multiple sclerosis in a laundry list of allegedly treatable conditions simply does not provide sufficient enabling disclosure to teach, suggest, or provide a reasonable expectation of success in achieving Applicants' claimed methods of treating demyelinating disorders using AMPA receptor inhibitors.

In the Advisory Action, the Examiner deemed unpersuasive the argument that Applicants were the first to recognize the glutamate ionotropic AMPA receptor as a target for the treatment of demyelinating disorders, because Applicants' work was published in Nature Medicine in 2000, which is after the § 102(e) date of Shishikura. The Examiner's assertion merely reemphasizes Applicants' non-obviousness arguments: if the subject matter of the present Application was first published in Nature Medicine in 2000, then Shishikura could not disclose or suggest the use of an AMPA receptor inhibitor for treating disorders induced by demyelination. The teachings of Shishikura are directed to the use of an AMPA receptor inhibitor for treating a neurological disorder caused by neurotoxicity. Information regarding the effect of the AMPA receptor on demyelination was only available after the § 102(e) date of Shishikura, as acknowledged by the Examiner.

Csuzdi teaches 2,3-benzodiazepine derivatives and their use as noncompetitive AMPA receptor inhibitors for treating neurological disorders. Csuzdi does not discuss

demyelinating disorders, and there is no teaching or suggestion that the disclosed 2,3-benzodiazepine derivatives could be used to treat demyelinating disorders. Instead, Csuzdi merely teaches that 2,3-benzodiazepine derivatives can be used to prevent the destruction of neurons.

Thus, Shishikura and Csuzdi, alone or in combination, do not teach or suggest the claimed methods of treating demyelinating disorders by administering inhibitors of the interaction of glutamate with the AMPA receptor complex. There is no teaching or suggestion in either reference that AMPA receptor antagonists interfere with the process of demyelination, nor is there any enabling disclosure that would provide one of ordinary skill in the art with a reasonable expectation of success in using AMPA receptor antagonists to treat demyelinating disorders as claimed.

Therefore, because Shishikura and Csuzdi do not teach or suggest every limitation of the claimed invention, or provide a reasonable expectation of success in achieving the claimed invention, claims 21-22 and 24-25 are not obvious over the cited references, alone or in combination. Accordingly, Applicants respectfully request reconsideration and withdrawal of the present rejection under § 103(a).

Rejection of claims 23, 29-30, and 38 under 35 U.S.C. § 103(a)

In the Advisory Action, the Examiner also maintained the rejection of Claims 23, 29-30, and 38 under 35 U.S.C. § 103(a) as allegedly being obvious over Shishikura in view of Csuzdi and further in view of Prineas et al., "Demyelinating Diseases," in Greenfield's Neuropathology, 813-896 (1997) ("Prineas"). Applicants respectfully traverse this rejection.

To support a *prima facie* case of obviousness, there must be some suggestion or motivation to combine the teachings of the cited references. The motivation to combine must be found in the prior art, and must not be based on impermissible hindsight in view of Applicants' disclosure. MPEP § 2142.

Applicants' claim 23 is directed to the treatment of certain secondary demyelinating disorders by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex. Claims 29-30 and 38 are directed to methods and

compositions for treating a demyelinating disorder by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex in combination with another agent.

As discussed above, the combined disclosures of Shishikura and Csuzdi merely teach one of ordinary skill in the art that AMPA receptor inhibitors can be used to treat neurodegenerative disorders and protect against kainic acid neuronal excitoxicity and seizures. These references do not teach or suggest the treatment of demyelinating diseases generally, or secondary demyelinating disorders in particular.

The Examiner argued that Prineas teaches (i) that interferon-β curtails immune activation by counteracting some of the proinflammatory actions of interferon-γ and reduces the rate of clinical relapses of multiple sclerosis, and (ii) the general pathological features of demyelinating disorders. However, Prineas does not disclose or suggest the treatment of demyelinating disorders with inhibitors of the interaction of glutamate with the AMPA receptor complex.

Thus, a *prima facie* case of obviousness has not been established, because the cited references in combination still do not teach or suggest the treatment of demyelinating disorders, and particularly secondary demyelinating disorders, by administering an inhibitor of the interaction of glutamate with the AMPA receptor complex, alone or in combination with another agent.

Furthermore, there would be no motivation to combine the teachings of the cited references, because they are directed to distinct subject areas. Specifically, there would be no motivation to combine the teachings of Shishikura and Csuzdi regarding agents for treating neurodegenerative diseases and preventing kainic acid neuronal excitoxicity and seizures with the teachings of Prineas, which relate to demyelinating diseases.

As described in Dr. Smith's declaration, there is no known relationship between the excitotoxicity addressed by Shishikura and cell death due to demyelination. Rather, Shishikura uses the effectiveness of pyridothiazine derivatives against seizures and kainic acid excitotoxicity, which do not belong to the symptomatology of demyelinating disorders, as evidence for usefulness in the treatment of multiple sclerosis. Multiple

sclerosis is addressed by Shishikura merely because its symptomatology includes spasticity (which is not necessarily associated with other demyelinating disorders), and AMPA antagonists were known to have muscle relaxant activity. Shishikura does not address multiple sclerosis as a demyelinating disorder, and does not teach or suggest usefulness of the disclosed compounds in treating demyelination. Thus, there would be no expectation that any compound which protects cells against excitotoxicity induced by kainic acid or against seizures as disclosed in Shishikura might be useful in therapy of demyelinating disorders generally, and certainly not in the particular secondary demyelinating disorders recited in Applicants' claim 23.

Because the teachings of Shishikura would not cause one of ordinary skill in the art to expect an inhibitor of the interaction of glutamate with the AMPA receptor complex to be useful in treating demyelinating disorders, there would be no motivation to administer such agents in combination with other agents for treating demyelinating disorders as recited in Applicants' claims 29-30 and 38. Indeed, the only possible motivation to combine the teachings of Shishikura and Csuzdi disclosing particular AMPA receptor antagonists for treating neurodegenerative diseases and protecting against neuronal excitoxicity with the teachings of Prineas regarding demyelinating disorders and agents for treating such disorders would be based on improper hindsight in view of Applicants' disclosure.

In sum, *prima facie* obviousness has not been established because the cited references do not teach or suggest every element of the claimed invention and there is no motivation to combine the teachings of the cited references. Thus, claims 23, 29-30, and 38 are not obvious over Shishikura, Csuzdi, and Prineas, alone or in combination, and Applicants respectfully submit that this rejection under § 103(a) should be reconsidered and withdrawn.

Conclusion

In view of the arguments set forth above and the declaration of Terence Smith submitted herewith, Applicants contend that all of the outstanding rejections have been

overcome and should be reconsidered and withdrawn. Applicants respectfully submit that all of the pending the claims are in condition for allowance.

Applicants hereby petition for a five-month extension of time pursuant to 37 C.F.R. § 1.136, until April 8, 2004, based on the Notice of Appeal received by the U.S. Patent and Trademark Office on September 8, 2003. Please deduct the $2,010.00 fee for this purpose from our Deposit Account No. 08-0219. Please deduct the $770.00 fee for the present Request for Continued Examination from our Deposit Account No. 08-0219 as well. No other fees are believed to be due in association with this submission. However, please charge any other payments due or credit any overpayments to our Deposit Account No. 08-0219.

The Examiner is invited to contact the undersigned at the telephone number below in order to expedite prosecution and allowance of this application.

Respectfully submitted,

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